METRC Policy & Procedure Manual

Title: Human Subjects Recruitment & Safety Procedures

General Description & Purpose: This document describes METRC's policies and procedures regarding recruitment and protection of human subjects in METRC studies.

I. Study Population & Eligibility Criteria

The study population and eligibility criteria for METRC studies are determined by the study PI and Protocol Committee. The study population specifies recruitment sites, both civilian and Military Treatment Facilities. The eligibility criteria include a comprehensive set of inclusion and exclusion criteria. The IRB approved master study protocol is the authority document for a given study's population and eligibility criteria.

II. Screening & Recruitment Process

The Study PI, Protocol Committee, and MCC Study Team for each study determine the study-specific procedures for screening and enrollment into METRC studies. These procedures are included in the study protocol; the IRB approved version of this document is considered the authority document for a given study's screening and recruitment plan.

METRC study screening and recruitment plans generally include, but are not limited to, the following content:

- Recruitment sites, e.g., *n* civilian sites and *n* Military Treatment Facilities
- Individuals at the sites who will identify eligible patients, e.g., orthopaedic attendings, research coordinators
- Thorough description of screening, inclusion, and exclusion criteria
- Timing of screening and/or eligibility determination, e.g., at time of definitive treatment
- Study-specific consent procedures (overarching METRC consent procedures described below) including timing of consent, e.g., prior to discharge from index hospitalization
- Enrollment procedures, e.g., assignment of study ID in REDCap, randomization in REDCap, etc.
- Description of participant remuneration and procedures for disbursing payments

III. Informed Consent Process

METRC has adopted a comprehensive informed consent process for all of its studies that involves the treating surgeon, the clinical site research coordinator(s), and informational materials and resources for patients and family members to facilitate informed decision making about participation. The goal of the consent process is to provide each eligible patient with sufficient information about the study, adequately address their questions and concerns and give them time to make an informed decision about whether to participate.

There are strong ethical and practical reasons for striving for a quality consent processes. The decision to participate in this study is completely voluntary; decisions to enroll made in haste, without adequate thought or reflection are not in the participant's nor investigator's interest. The consent process is one of the more important participant-investigator interactions as it serves not only to inform the potential research participant, but also as a trust-building and bonding experience. The rapport and relationship between the research participant and clinical investigator is of particular importance in longitudinal

studies where the research participants will be called upon to fulfill their commitment to the research study beyond the time during which they would standardly engage with the clinician investigator.

Informed Consent Templates

The study team for each study uses the appropriate Informed Consent Template when developing the Master/ Parent Study Consent Form. Different IRBs have different Informed Consent Form templates. A copy of the Johns Hopkins School of Medicine Single IRB Informed Consent Form template is provided as an example. The METRC study team confirms the versioning of a given template before developing the study-specific document.

IV. Recruitment & Enrollment Materials

Recruitment and enrollment materials are developed in conjunction with the Protocol Committee and consultants as appropriate to ensure that the materials are accessible, informative, and culturally sensitive. METRC works with experts in research ethics affiliated with the Institute for Clinical and Translational Research at Johns Hopkins (the institution's CTSA) in this process as needed.

V. Risk and Benefits Assessment

The study PI, Protocol Committee, and MCC Study Team complete and document a risks and benefits assessment for each METRC study. This information is included in the study protocol and study-specific Informed Consent Form. The IRB approved versions of these documents are considered to be the authority documents.

VI. Risk Management & Emergency Response

The study PI, Protocol Committee, and MCC Study Team develop a study-specific risk management and emergency response plan. At a minimum, these plans identify and define:

- What constitutes a reportable event
- Required timelines for reporting events
- Procedures for reporting the events in REDCap or other format as applicable
- How event reporting forms are programmed into the study database such that automated notifications are distributed to the appropriate people, e.g., the Medical Monitor, the study PIs, etc.
- Timeline and procedures associated with Medical Monitor review of reported information
- How Medical Monitor communicates decisions regarding relatedness and actions that should be taken to ensure safety and protocol adherence
- How events are reported to the IRB, DoD HRPO, or other required agencies, e.g., the FDA
- Actions taken by the MCC in the event that a SAE demonstrates increased risk of study participation, including pausing the study, modifying the protocol, or even terminating the study protocol

Medical Monitor

To protect the safety of study participants, an independent Medical Monitor is appointed for each randomized METRC trial. This individual prospectively reviews SAEs that are reported in real-time via REDCap and makes a determination for how they should be handled within 24 hours of notification.

VII. DSMB

METRC established an independent Data Safety Monitoring Board (DSMB) to monitor its randomized trials. Prior to the initiation of new randomized studies, the DSMB reviews the study protocol, informed

consent documents and plans for safety and monitoring and makes recommendations to the study PI to address concerns if any are raised.

Throughout the study period, the DSMB is responsible for evaluating the progress of the trial, including biannual assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, site performance and other factors that can affect study outcome, as well as ensuring the confidentiality of the trial data and study results. In evaluating study progress, the DSMB considers factors external to the study when relevant information becomes available such as scientific or therapeutic developments that may have an impact on the safety of participants or the ethics of the trial. As appropriate, the DSMB reviews interim analyses conducted by the Coordinating Center under the direction of the lead biostatisticians in accordance with stopping rules which are clearly defined in advance of data analysis and have approval by the DSMB.

After each DSMB meeting, the Chair makes recommendations to the DoD, the Consortium Committee and, as required, the FDA, concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study. The Chair also assists the Coordinating Center by commenting on any problems with study conduct, enrollment, sample size and/or data collection and makes recommendations to assist in the resolution of problems related to clinical site performance. The Chair's recommendations are documented in formal, study-specific letters which are submitted to the IRB at Continuing Review, circulated to participating sites, and posted to the Study Materials section of the METRC website.

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